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(54) Title: METALLOPROTEINASE INHIBITORS

(57) Abstract: Compounds of the formula (I) useful as metalloproteinase inhibitors, especially as inhibitors of MMP12, wherein R5 is a monocyclic group.

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Metalloproteinase inhibitors

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising these, as well as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes. Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMPs) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many diseases or conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these diseases

or conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atherosclerosis; asthma; rhinitis; and chronic obstructive pulmonary diseases (COPD).

MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* (1992, Journal of Biological Chemistry 267: 4664) and in man by the same group in 1995. MMP-12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers (Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824) as well as in foam cells in atherosclerotic lesions (Matsumoto *et al*, 1998, Am J Pathol 153: 109). A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wildtype mice developed pulmonary emphysema after this treatment. When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP-12 is a key enzyme in the COPD pathogenesis. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that smoking increases macrophage infiltration and macrophage-derived MMP-12 expression

in human carotid artery plaques Kangavari (Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000).

MMP13, or collagenase 3, was initially cloned from a cDNA library derived from a breast tumour [J. M. P. Freije *et al.* (1994) Journal of Biological Chemistry 269(24):16766-16773]. PCR-RNA analysis of RNAs from a wide range of tissues indicated that MMP13 expression was limited to breast carcinomas as it was not found in breast fibroadenomas, normal or resting mammary gland, placenta, liver, ovary, uterus, prostate or parotid gland or in breast cancer cell lines (T47-D, MCF-7 and ZR75-1). Subsequent to this observation MMP13 has been detected in transformed epidermal keratinocytes [N. Johansson *et al.*, (1997) Cell Growth Differ. 8(2):243-250], squamous cell carcinomas [N. Johansson *et al.*, (1997) Am. J. Pathol. 151(2):499-508] and epidermal tumours [K. Airola *et al.*, (1997) J. Invest. Dermatol. 109(2):225-231]. These results are suggestive that MMP13 is secreted by transformed epithelial cells and may be involved in the extracellular matrix degradation and cell-matrix interaction associated with metastasis especially as observed in invasive breast cancer lesions and in malignant epithelia growth in skin carcinogenesis.

Recent published data implies that MMP13 plays a role in the turnover of other connective tissues. For instance, consistent with MMP13's substrate specificity and preference for degrading type II collagen [P. G. Mitchell *et al.*, (1996) J. Clin. Invest. 97(3):761-768; V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550], MMP13 has been hypothesised to serve a role during primary ossification and skeletal remodelling [M. Stahle-Backdahl *et al.*, (1997) Lab. Invest. 76(5):717-728; N. Johansson *et al.*, (1997) Dev. Dyn. 208(3):387-397], in destructive joint diseases such as rheumatoid and osteo-arthritis [D. Wernicke *et al.*, (1996) J. Rheumatol. 23:590-595; P. G. Mitchell *et al.*, (1996) J. Clin. Invest. 97(3):761-768; O. Lindy *et al.*, (1997) Arthritis Rheum 40(8):1391-1399]; and during the aseptic loosening of hip replacements [S. Imai *et al.*, (1998) J. Bone Joint Surg. Br. 80(4):701-710]. MMP13 has also been implicated in chronic adult periodontitis as it has been localised to the epithelium of chronically inflamed mucosa human gingival tissue [V. J. Uitto *et al.*, (1998) Am. J. Pathol

152(6):1489-1499] and in remodelling of the collagenous matrix in chronic wounds [M. Vaalamo *et al.*, (1997) J. Invest. Dermatol. 109(1):96-101].

MMP9 (Gelatinase B; 92kDa TypeIV Collagenase; 92kDa Gelatinase) is a secreted protein which was first purified, then cloned and sequenced, in 1989 [S.M. Wilhelm *et al* (1989) J. Biol Chem. 264 (29): 17213-17221; published erratum in J. Biol Chem. (1990) 265 (36): 22570]. A recent review of MMP9 provides an excellent source for detailed information and references on this protease: T.H. Vu & Z. Werb (1998) (In : Matrix Metalloproteinases. 1998. Edited by W.C. Parks & R.P. Mecham. pp115 - 148. Academic Press. ISBN 0-12-545090-7). The following points are drawn from that review by T.H. Vu & Z. Werb (1998).

The expression of MMP9 is restricted normally to a few cell types, including trophoblasts, osteoclasts, neutrophils and macrophages. However, it's expression can be induced in these same cells and in other cell types by several mediators, including exposure of the cells to growth factors or cytokines. These are the same mediators often implicated in initiating an inflammatory response. As with other secreted MMPs, MMP9 is released as an inactive Pro-enzyme which is subsequently cleaved to form the enzymatically active enzyme. The proteases required for this activation *in vivo* are not known. The balance of active MMP9 versus inactive enzyme is further regulated *in vivo* by interaction with TIMP-1 (Tissue Inhibitor of Metalloproteinases -1), a naturally-occurring protein. TIMP-1 binds to the C-terminal region of MMP9, leading to inhibition of the catalytic domain of MMP9. The balance of induced expression of ProMMP9, cleavage of Pro- to active MMP9 and the presence of TIMP-1 combine to determine the amount of catalytically active MMP9 which is present at a local site. Proteolytically active MMP9 attacks substrates which include gelatin, elastin, and native Type IV and Type V collagens; it has no activity against native Type I collagen, proteoglycans or laminins.

There has been a growing body of data implicating roles for MMP9 in various physiological and pathological processes. Physiological roles include the invasion of embryonic trophoblasts through the uterine epithelium in the early stages of embryonic

implantation; some role in the growth and development of bones; and migration of inflammatory cells from the vasculature into tissues.

MMP-9 release, measured using enzyme immunoassay, was significantly enhanced in fluids and in AM supernatants from untreated asthmatics compared with those from other populations [Am. J. Resp. Cell & Mol. Biol., (Nov 1997) 17 (5):583-591]. Also, increased MMP9 expression has been observed in certain other pathological conditions, thereby implicating MMP9 in disease processes such as COPD, arthritis, tumour metastasis, Alzheimer's, Multiple Sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as Myocardial Infarction.

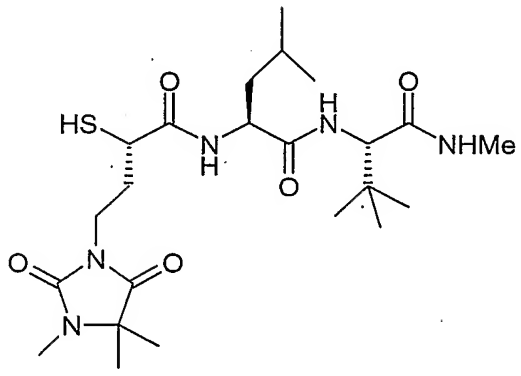
MMP-8 (collagenase-2, neutrophil collagenase) is a 53 kD enzyme of the matrix metalloproteinase family that is preferentially expressed in neutrophils. Later studies indicate MMP-8 is expressed also in other cells, such as osteoarthritic chondrocytes [Shlopov *et al*, (1997) Arthritis Rheum, 40:2065]. MMPs produced by neutrophils can cause tissue remodelling, and hence blocking MMP-8 should have a positive effect in fibrotic diseases of for instance the lung, and in degradative diseases like pulmonary emphysema. MMP-8 was also found to be up-regulated in osteoarthritis, indicating that blocking MMP-8 may also be beneficial in this disease.

MMP-3 (stromelysin-1) is a 53 kD enzyme of the matrix metalloproteinase enzyme family. MMP-3 activity has been demonstrated in fibroblasts isolated from inflamed gingiva [Uitto V. J. *et al*, (1981) J. Periodontal Res., 16:417-424], and enzyme levels have been correlated to the severity of gum disease [Overall C. M. *et al*, (1987) J. Periodontal Res., 22:81-88]. MMP-3 is also produced by basal keratinocytes in a variety of chronic ulcers [Saarialho-Kere U. K. *et al*, (1994) J. Clin. Invest., 94:79-88]. MMP-3 mRNA and protein were detected in basal keratinocytes adjacent to but distal from the wound edge in what probably represents the sites of proliferating epidermis. MMP-3 may thus prevent the epidermis from healing. Several investigators have demonstrated consistent elevation of MMP-3 in synovial fluids from rheumatoid and osteoarthritis patients as compared to controls [Walakovits L. A. *et al*, (1992) Arthritis Rheum., 35:35-42; Zafarullah M. *et al*, (1993) J. Rheumatol., 20:693-697]. These studies provided the basis for the belief that an

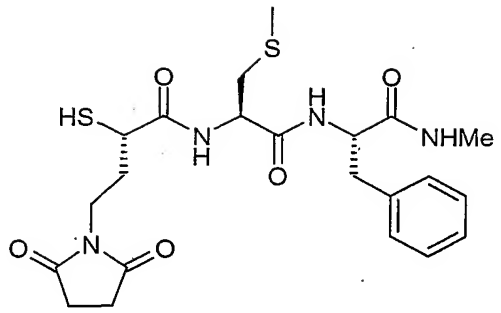
inhibitor of MMP-3 will treat diseases involving disruption of extracellular matrix resulting in inflammation due to lymphocytic infiltration, or loss of structural integrity necessary for organ function.

A number of metalloproteinase inhibitors are known (see for example the review of MMP inhibitors by Beckett R.P. and Whittaker M., 1998, Exp. Opin. Ther. Patents, 8(3):259-282). Different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases.

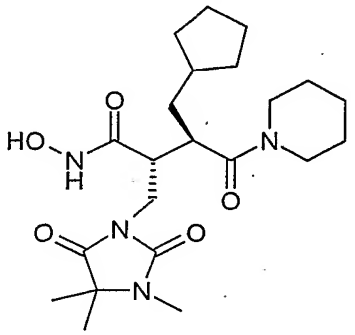
Whittaker M. *et al* (1999, Chemical Reviews 99(9):2735-2776) review a wide range of known MMP inhibitor compounds. They state that an effective MMP inhibitor requires a zinc binding group or ZBG (functional group capable of chelating the active site zinc(II) ion), at least one functional group which provides a hydrogen bond interaction with the enzyme backbone, and one or more side chains which undergo effective van der Waals interactions with the enzyme subsites. Zinc binding groups in known MMP inhibitors include carboxylic acid groups, hydroxamic acid groups, sulfhydryl or mercapto, etc. For example, Whittaker M. *et al* discuss the following MMP inhibitors:



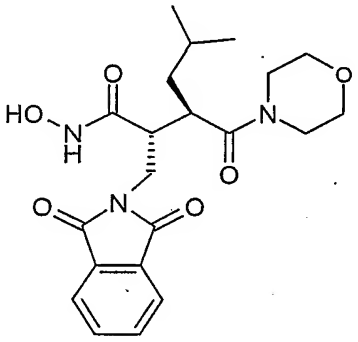
The above compound entered clinical development. It has a mercaptoacyl zinc binding group, a trimethylhydantoinylethyl group at the P1 position and a leucinyl-*tert*-butyllglycinyl backbone.



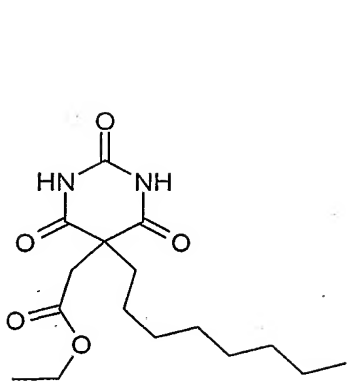
The above compound has a mercaptoacyl zinc binding group and an imide group at the P1 position.

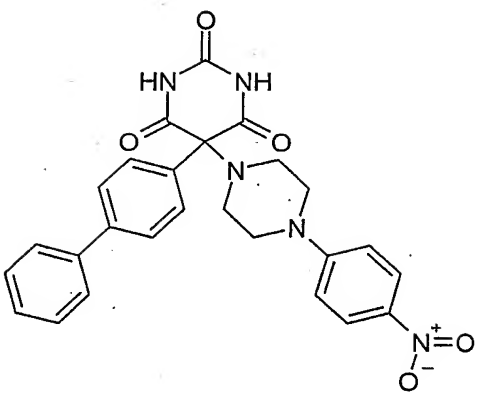


The above compound was developed for the treatment of arthritis. It has a non-peptidic succinyl hydroxamate zinc binding group and a trimethylhydantoinylethyl group at the P1 position.



The above compound is a phthalimido derivative that inhibits collagenases. It has a non-peptidic succinyl hydroxamate zinc binding group and a cyclic imide group at P1. Whittaker M. *et al* also discuss other MMP inhibitors having a P1 cyclic imido group and various zinc binding groups (succinyl hydroxamate, carboxylic acid, thiol group, phosphorous-based group).

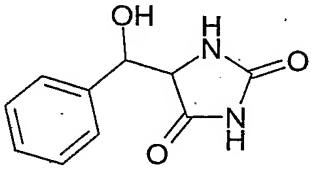




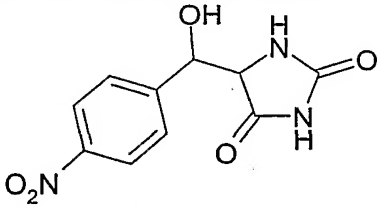
The above compounds appear to be good inhibitors of MMP8 and MMP9 (PCT patent applications WO9858925, WO9858915). They have a pyrimidin-2,3,4-trione zinc binding group.

The following compounds are not known as MMP inhibitors:-

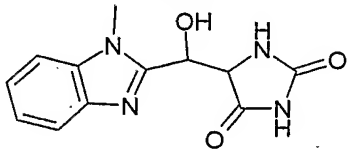
Japanese patent number 5097814 (1993) describes a method of preparing compounds useful as intermediates for production of antibiotics, including the compound having the formula:



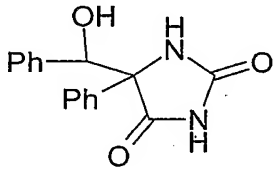
Morton *et al* (1993, J Agric Food Chem 41(1): 148-152) describe preparation of compounds with fungicidal activity, including the compound having the formula:

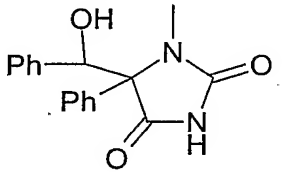


Dalgatov, D *et al* (1967, Khim. Geterotsikl. Soedin. 5:908-909) describe synthesis of the following compound without suggesting a use for the compound:

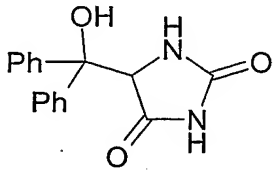


Crooks, P *et al* (1989, J. Heterocyclic Chem. 26(4):1113-17) describe synthesis of the following compounds that were tested for anticonvulsant activity in mice:

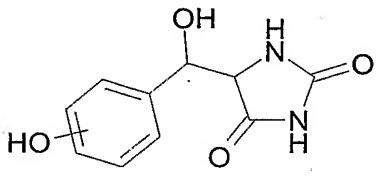


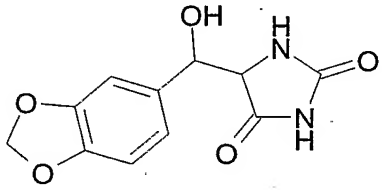


Gramain, J.C *et al* (1990) Recl. Trav. Chim. Pays-Bas 109:325-331) describe synthesis of the following compound:

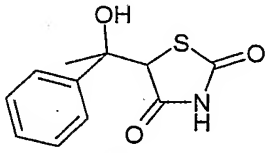


Japanese patent number 63079879 (1988) describes a method for the synthesis of intermediates en route to important amino acids. The following compounds have been used as starting materials:

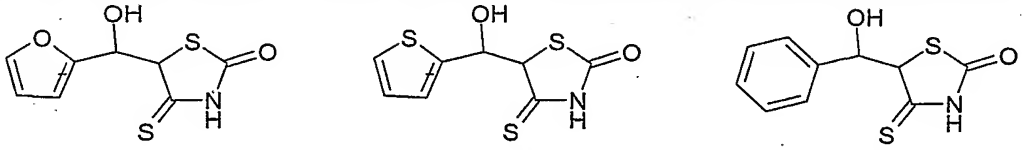




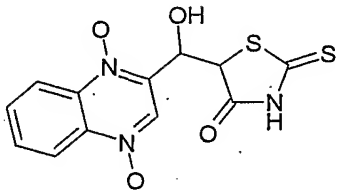
Wolfe, J *et al* (1971, Synthesis 6:310-311) describe synthesis of the following compound without suggesting a use for the compound:



Moharram *et al* (1983, Egypt J. Chem. 26:301-11) describe the following compounds:

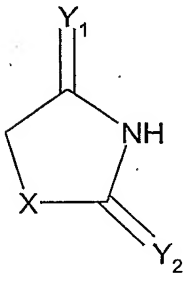


Hungarian patent number 26403 (1983) describes the synthesis and use as food additive of the following compound :



We have now discovered a new class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting MMPs such as MMP-12. The compounds are metalloproteinase inhibitors having a metal binding group that is not found in known metalloproteinase inhibitors. In particular, we have discovered compounds that are potent MMP12 inhibitors and have desirable activity profiles. The compounds of this invention have beneficial potency, selectivity and/or pharmacokinetic properties.

The metalloproteinase inhibitor compounds of the invention comprise a metal binding group and one or more other functional groups or side chains characterised in that the metal binding group has the formula (k)



(k)

wherein X is selected from NR1, O, S;

Y1 and Y2 are independently selected from O, S;

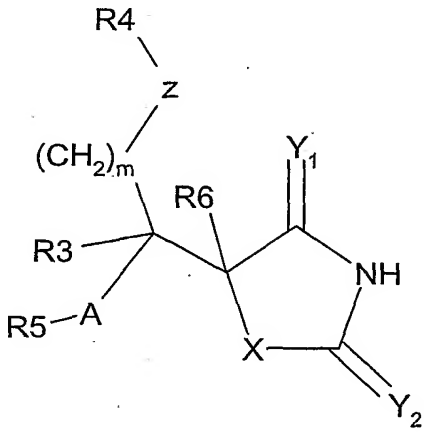
R1 is selected from H, alkyl, haloalkyl;

Any alkyl groups outlined above may be straight chain or branched; any alkyl group outlined above is preferably (C1-7)alkyl and most preferably (C1-6)alkyl.

A metalloproteinase inhibitor compound is a compound that inhibits the activity of a metalloproteinase enzyme (for example, an MMP). By way of non-limiting example the inhibitor compound may show IC50s *in vitro* in the range of 0.1-10000 nanomolar, preferably 0.1-1000 nanomolar.

A metal binding group is a functional group capable of binding the metal ion within the active site of the enzyme. For example, the metal binding group will be a zinc binding group in MMP inhibitors, binding the active site zinc(II) ion. The metal binding group of formula (k) is based on a five-membered ring structure and is preferably a hydantoin group, most preferably a -5 substituted 1-H,3-H-imidazolidine-2,4-dione.

In a first aspect of the invention we now provide compounds of the formula I



I

wherein

X is selected from NR1, O, S;

Y1 and Y2 are independently selected from O, S;

Z is selected from NR2, O, S;

m is 0 or 1;

A is selected from a direct bond, (C1-6)alkyl, (C1-6)alkenyl, (C1-6)haloalkyl, or (C1-6)heteroalkyl containing a hetero group selected from N, O, S, SO, SO2 or containing two hetero groups selected from N, O, S, SO, SO2 and separated by at least two carbon atoms;

R1 is selected from H, alkyl, haloalkyl;

R2 is selected from H, alkyl, haloalkyl;

R3 and R6 are independently selected from H, halogen (preferably F), alkyl, haloalkyl, alkoxyalkyl, heteroalkyl, cycloalkyl, aryl, alkylaryl, heteroalkyl-aryl, heteroaryl, alkylheteroaryl, heteroalkyl-heteroaryl, arylalkyl, aryl-heteroalkyl, heteroaryl-alkyl, heteroaryl-heteroalkyl, bisaryl, aryl-heteroaryl, heteroaryl-aryl, bisheteroaryl, cycloalkyl or heterocycloalkyl comprising 3 to 7 ring atoms, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl radicals may be optionally substituted by one or more groups independently selected from hydroxy, alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, carboxy,
carboxyalkyl, alkylcarboxy, amino, N-alkylamino, N,N-dialkylamino, alkylamino, alkyl(N-alkyl)amino, alkyl(N,N-dialkyl)amino, amido, N-alkylamido, N,N-dialkylamido, alkylamido, alkyl(N-alkyl)amido, alkyl(N,N-dialkyl)amido, thiol, sulfone, sulfonamino, alkylsulfonamino, arylsulfonamino, sulfonamido, haloalkyl sulfone, alkylthio, arylthio, alkylsulfone, arylsulfone, aminosulfone, N-alkylaminosulfone, N,N-dialkylaminosulfone, alkylaminosulfone, arylaminosulfone, cyano, alkylcyano, guanidino, N-cyano-guanidino, thioguanidino, amidino, N-aminosulfon-amidino, nitro, alkylnitro, 2-nitro-ethene-1,1-diamine;

R4 is selected from H, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, haloalkoxy, aminoalkyl, amidoalkyl, thioalkyl;

R5 is a monocyclic group comprising 3 to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, optionally substituted by one or more substituents independently selected from halogen, hydroxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, cyano, nitro, alkyl, alkoxy, alkyl sulfone, haloalkyl sulfone, carbonyl, carboxy, wherein any alkyl radical within any substituent may itself be

optionally substituted with one or more groups selected from halogen, hydroxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfono, alkylaminosulfono, alkylcarboxylate, amido, N-alkylamido, N,N-dialkylamido, alkoxy, haloalkoxy, carbonyl, carboxy;

Any heteroalkyl group outlined above is a hetero atom-substituted alkyl containing one or more hetero groups independently selected from N, O, S, SO, SO2, (a hetero group being a hetero atom or group of atoms);

Any heterocycloalkyl or heteroaryl group outlined above contains one or more hetero groups independently selected from N, O, S, SO, SO2;

Any alkyl, alkenyl or alkynyl groups outlined above may be straight chain or branched; unless otherwise stated, any alkyl group outlined above is preferably (C1-7)alkyl and most preferably (C1-6)alkyl;

Provided that:

when X is NR1, R1 is H, Y1 is O, Y2 is O, Z is O, m is 0, A is a direct bond, R3 is H, R4 is H and R6 is H, then R5 is not phenyl, nitrophenyl, hydroxyphenyl, alkoxyphenyl or pyridine;

when X is NR1, R1 is H or methyl, Y1 is O, Y2 is O, Z is O, m is 0, A is a direct bond, R3 is H, R4 is H and R6 is phenyl, then R5 is not phenyl;

when X is NR1, R1 is H, Y1 is O, Y2 is O, Z is O, m is 0, A is a direct bond, R3 is phenyl, R4 is H and R6 is H, then R5 is not phenyl;

when X is S, at least one of Y1 and Y2 is O, m is 0, A is a direct bond, R3 is H or methyl, R6 is H or methyl, then R5 is not phenyl, pyridine, pyrrole, thiophen or furan;

when X is O, Y1 is O, Y2 is O, Z is O, m is 0, A is a direct bond, R3 is methylchloride, R4 is H and R6 is H, then R5 is not phenyl.

Preferred compounds of the formula I are those wherein any one or more of the following apply:

X is NR1;

At least one of Y1 and Y2 is O; especially both Y1 and Y2 are O;

Z is O;

m is 0;

A is a direct bond;

R1 is H, (C1-3)alkyl or (C1-3)haloalkyl; especially R1 is H or (C1-3)alkyl; most especially R1 is H;

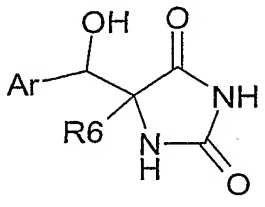
R3 is H, alkyl or haloalkyl; especially R3 is H , (C1-6)alkyl or (C1-6)haloalkyl; most especially R3 is H;

R4 is H, alkyl or haloalkyl; especially R4 is H , (C1-6)alkyl or (C1-6)haloalkyl; most especially R4 is H;

R5 is an optionally substituted 5 or 6 membered ring independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl; especially R5 is a 5 or 6 membered aryl or heteroaryl;

R6 is H, alkyl, hydroxyalkyl, aminoalkyl, cycloalkyl-alkyl, alkyl-cycloalkyl, arylalkyl, alkylaryl, heteroalkyl, heterocycloalkyl-alkyl, alkyl-heterocycloalkyl, heteroaryl-alkyl or heteroalkyl-aryl; especially R6 is alkyl, aminoalkyl or heteroaryl-alkyl.

Particular compounds of the invention include compounds of formula II:



Formula II

wherein

Ar is a 5 or 6 membered aryl or heteroaryl group optionally substituted by one or two substituents selected from halogen, amino, nitro, (C1-6)alkyl, (C1-6)alkoxy or (C1-6) haloalkoxy;

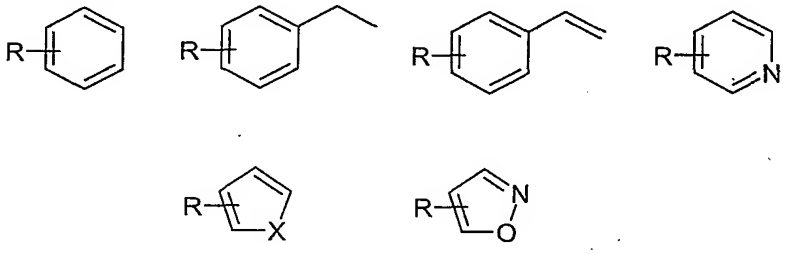
R6 is selected from H, aryl or (C1-6)alkyl and R6 is optionally substituted by a group selected from hydroxy, thioalkyl, phenyl, halophenyl, pyridyl or carbamate.

Preferred compounds of the formula II are those wherein any one or more of the following apply:

Ar is phenyl or substituted phenyl, especially a phenyl substituted by one or two halogens; or Ar is a 5-membered heteroaryl ring comprising two heteroatoms independently selected from O and N;

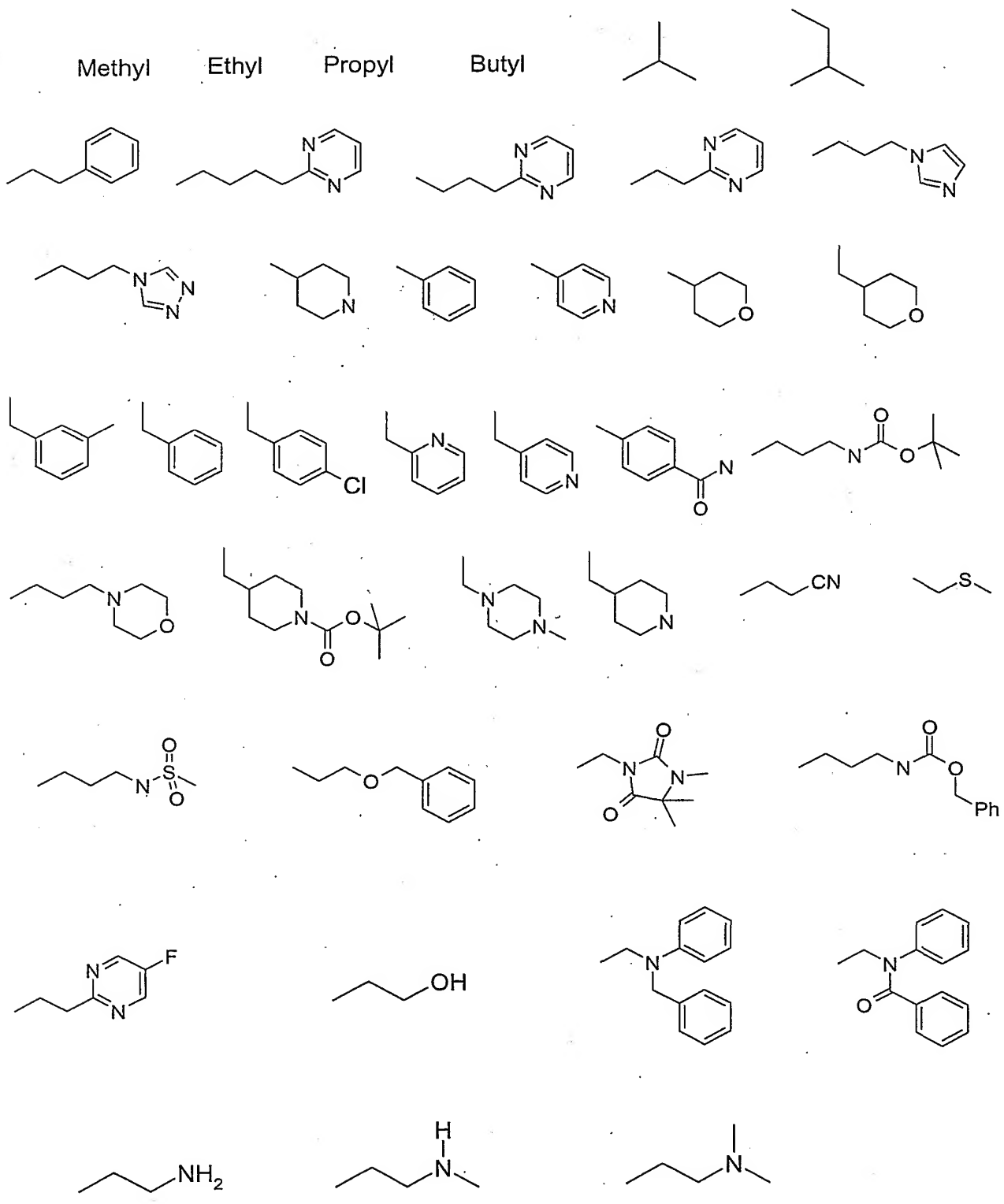
R6 is phenyl, phenyl substituted with a halogen, methylene pyridine, or (C1-3)alkyl optionally substituted with hydroxy, thiomethyl or benzyl carbamate.

Suitable values for R5 in compounds of formula I or for Ar in compounds of formula II include:



R= H, (C1-6)alkyl, OH, CH3O, CF3, CF3O, F, Cl, Br, I
X= O, S or N

Suitable values for R6 in compounds of formula I or formula II include the following:


Methyl
Ethyl
Propyl
Butyl
N
O
Cl
CN
S
F
OH
NH2
H
Ph

It will be appreciated that the particular substituents and number of substituents in compounds of formula I or formula II are selected so as to avoid sterically undesirable combinations.

Each exemplified compound represents a particular and independent aspect of the invention.

Where optically active centres exist in the compounds of formula I or formula II, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates. Racemates may be separated into individual optically active forms using known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J March, p104-107) including for example the formation of diastereomeric derivatives having convenient optically active auxiliary species followed by separation and then cleavage of the auxiliary species.

It will be appreciated that the compounds according to the invention may contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres (chiral centres) in a compound of formula I or formula II can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

Where tautomers exist in the compounds of formula I or formula II, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

As previously outlined the compounds of the invention are metalloproteinase inhibitors, in particular they are inhibitors of MMP12. Each of the above indications for the compounds of the formula I or formula II represents an independent and particular embodiment of the invention.

Certain compounds of the invention are of particular use as inhibitors of MMP13 and/or MMP9 and/or MMP8 and/or MMP3. Certain compounds of the invention are of particular use as aggrecanase inhibitors ie. inhibitors of aggrecan degradation.

Compounds of the invention show a favourable selectivity profile. Whilst we do not wish to be bound by theoretical considerations, the compounds of the invention are believed to show selective inhibition for any one of the above indications relative to any MMP1 inhibitory activity, by way of non-limiting example they may show 100-1000 fold selectivity over any MMP1 inhibitory activity.

The compounds of the invention may be provided as pharmaceutically acceptable salts. These include acid addition salts such as hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine.

They may also be provided as *in vivo* hydrolysable esters. These are pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable *in vivo* hydrolysable esters for carboxy include methoxymethyl and for hydroxy include formyl and acetyl, especially acetyl.

In order to use a metalloproteinase inhibitor compound of the invention (a compound of the formula I or formula II) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect we provide a pharmaceutical composition which comprises a compound of the invention (a compound of the formula I or formula II) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof and pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal adminstration or by inhalation. For these

purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably of 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease or condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

Therefore in a further aspect, we provide a compound of the formula I or formula II or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in a method of therapeutic treatment of the human or animal body or for use as a therapeutic agent. We disclose use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes. In particular we disclose use in the treatment of a disease or condition mediated by MMP12 and/or MMP13 and/or MMP9 and/or MMP8 and/or MMP3 and/or aggrecanase; especially use in the treatment of a disease or condition mediated by MMP12 or MMP9; most especially use in the treatment of a disease or condition mediated by MMP12.

In yet a further aspect we provide a method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a

therapeutically effective amount of a compound of the formula I or formula II or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof. We also disclose the use of a compound of the formula I or formula II or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes.

Metalloproteinase mediated diseases or conditions include asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and Multiple Sclerosis (MS), hematological disorders.

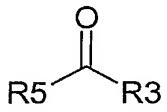
Preparation of the compounds of the invention

In another aspect the present invention provides processes for preparing a compound of the formula I or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as described in (a) to (g) below (X, Y1, Y2, Z, m, A and R1-R6 are as hereinbefore defined for the compound of formula I).

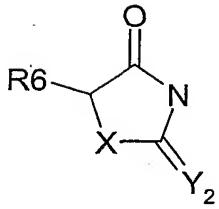
(a) A compound of formula I may be converted to a salt, especially a pharmaceutically acceptable salt, or vice versa, by known methods; a salt, especially a pharmaceutically acceptable salt, of a compound of formula I may be converted into a different salt, especially a pharmaceutically acceptable salt, by known methods.

(b) Compounds of formula I in which Z= O and R4= H may be prepared by reacting a compound of the formula IIa with a compound of the formula IIIa or a suitably protected form of a compound of formula IIIa (as shown in Scheme 1), and optionally thereafter forming a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof:

Scheme 1



IIa



IIIa

Aldehydes or ketones of formula IIa and compounds of formula IIIa in a suitable solvent are treated with a base, preferably in the temperature range from ambient temperature to reflux. Preferred base-solvent combinations include aliphatic amines such as trimethylamine, pyrrolidine or piperidine in solvents such as methanol, ethanol, tetrahydrofurane, acetonitrile or dimethylformamide, with addition of water when necessary to dissolve the reagents (Phillips, AP and Murphy, JG, 1951, J. Org. Chem. 16); or lithiumhexamethyldisilazan in tetrahydrofurane (Mio, S *et al,* 1991, Tetrahedron 47:2121-2132); or barium hydroxide octahydrate in isopropanol-water (Ajinomoto KK, 1993, Japanese Patent Number 05097814).

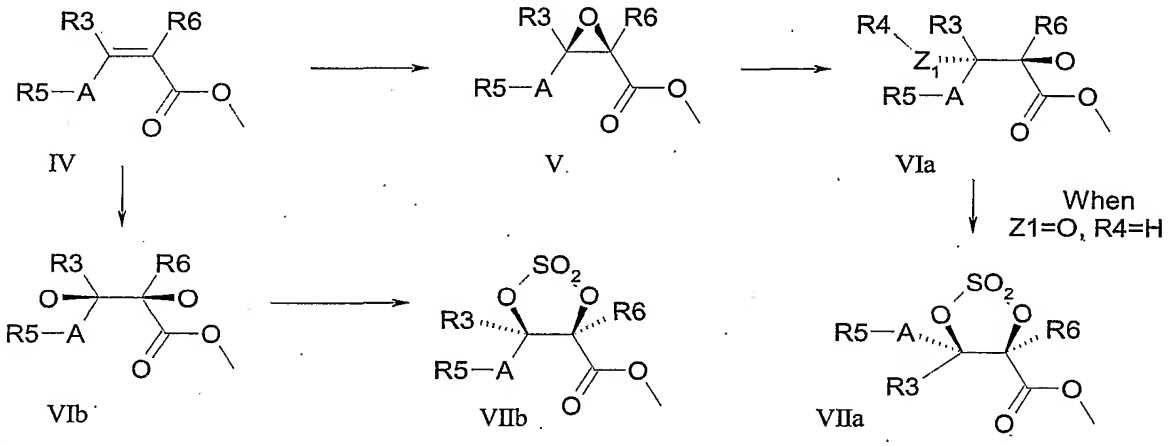
Preferably, when preparing compounds of formula I by this process, R3, R5 or R6 will not contain additional functionalities such as aldehydes, ketones, halogenated radicals or any other radicals well known to those skilled in the art which have the potential of interfering with, competing with or inhibiting the bond formation reaction.

It will be appreciated that many of the relevant starting materials are commercially or otherwise available or may be synthesised by known methods or may be found in the scientific literature.

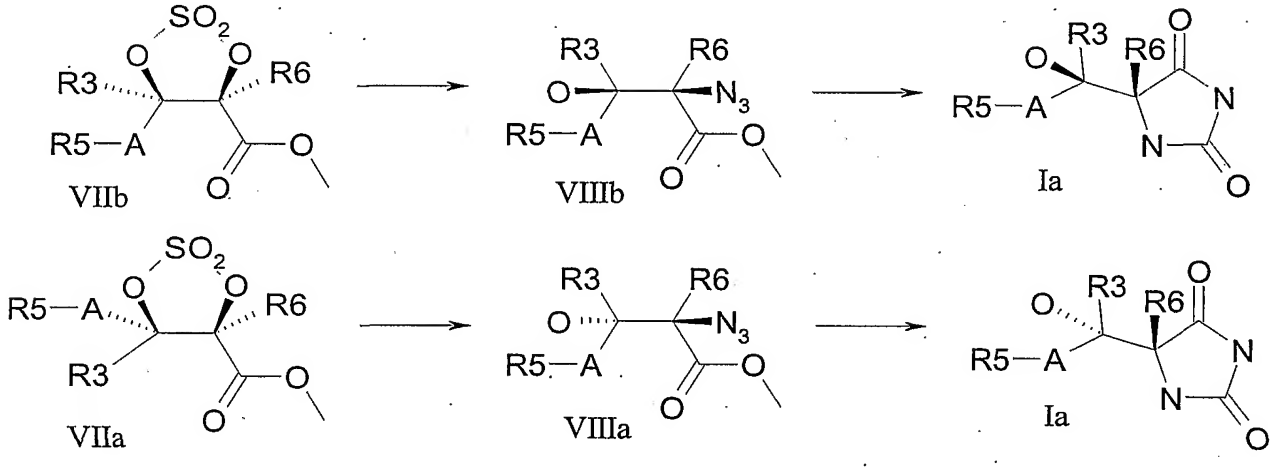
To prepare compounds of the general formula IIIa (R6 as hereinbefore described), compounds of formula IIIa in which R6 is H may be reacted with an appropriate aldehyde or ketone followed by dehydration and subsequent reduction of the resulting double bond by methods which are well know to those skilled in the art.

(c) Compounds of the formula I in which Z = O, R4 = H and X= N or NR1, especially specific stereoisomers thereof, may also be prepared as described for two of the four possible stereoisomers in Schemes 2 and 3 below.

Scheme 2



Scheme 3



Starting from the propenoate derivatives of formula IV, via the diols VIa or VIb by either asymmetric epoxidation followed by regioselective opening with water, or asymmetric dihydroxylation. Depending on the chiral auxiliary in the epoxidation or dihydroxylation, either the shown stereoisomers or their enantiomers of the diols of formula VIa or VIb can be obtained. (For example, Ogino, Y. *et al,* 1991, Tetrahedron

Lett. 32 (41):5761-5764; Jacobsen, E. N. *et al*, 1994, Tetrahedron, 50(15):4323-4334; Song, C. E. *et al, 1997,* Tetrahedron Asymmetry, 8 (6):841-844). Treatment with organic base and thionyl chloride and subsequent ruthenium tetroxide catalysed oxidation yields the cyclic sulfates VIIa and VIIb.

The cyclic sulfates of formula VIIa and VIIb are converted to the hydroxy azides (Scheme 3) of formula VIIIa and VIIIb by treatment with sodium azide in dimethylformamide followed by careful hydrolysis of the hemisulfate intermediates before aqueous work-up. (Gao, Sharpless, 1988, J.Am.Chem.Soc., 110:7538; Kim, Sharpless, 1989, Tetrahedron Lett., 30:655). The hydroxy azides of formula VIIIa and VIIIb are hydrolysed and reduced to the β-hydroxy-α-amino acids (not shown in Scheme 3), preferably hydrolysis with LiOH in THF followed by reduction with hydrogen sulfide, magnesium in methanol or organic phosphines by the Staudinger procedure. The β-hydroxy-α-amino acids in turn yield compounds of formula Ia upon treatment with cyanate and acid in aqueous media.

(d) Compounds of formula I in which Z =O and R4 is not H, especially specific stereoisomers thereof, may also be prepared as described for two of the four possible stereoisomers in Schemes 2 and 3. The compounds may be prepared by reacting the epoxides of formula V in Scheme 2 with an alcohol of formula R4-OH, yielding the alcohols Via. Subsequent conversion to the azides with phosphoazidate (Thompson, A. S. *et al,* 1993, J. Org. Chem. 58(22):5886-5888) yields the ether analogs of the azido esters VIIIa in Scheme 3, which can be carried through to the final products as described under process (c). The radical R4 in alcohols R4-OH and the radicals R3, R5 and R6 may be suitably protected. The protecting groups can be removed as a last step after the conversion to the hydantoins of formula I.

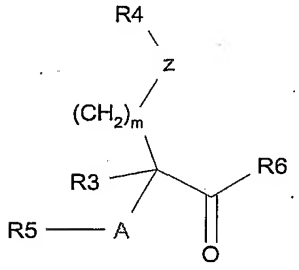
(e) Compounds of formula I in which Z is S or NR2 and Y1 and/or Y2 is O, especially specific stereoisomers thereof, may also be prepared as described for two of the four possible stereoisomers in Schemes 2 and 3. The compounds may be synthesised by opening of the epoxides of formula V (Scheme2) with thiols R4-SH or amines R4-NH_2 and thereafter subjected to analogous transformations as described for the alcohols VIIIa and

VIIIb in Scheme 3. When amines of R4-NH2 are used, it may be necessary to N-protect the intermediate amino alcohols, especially when the radical R4 is a n-alkyl group.

(f) Compounds of formula I in which X is S and Y1 and/or Y2 is O, especially specific stereoisomers thereof, may also be prepared as described for two of the four possible stereoisomers in Schemes 2 and 3. The compounds may be prepared by reacting the cyclic sulfates of formula VIIa or VIIb, or the α-hydroxy esters of formula VIa via their sulfonate esters, with thiourea and acid (1997, Japanese Patent number 09025273).

The propenoate derivatives of formula IV are widely accessible, eg from aldehydes and phosphonium or phosphonate derivatives of acetic acid via the Wittig or Horner-Emmons reaction (for example, van Heerden, P. S. *et al*, 1997, J. Chem. Soc., Perkin Trans. 1(8):141-1146).

(g) Compounds of formula I in which X=NR1 and R1=H may be prepared from reacting an appropriate substituted aldehyde or ketone of formula IId with ammonium carbonate and potassium cyanide in aqueous alcohols at 50-100°C in a sealed vessel for 4-24h.



IId

The compounds of the invention may be evaluated for example in the following assays:

Isolated Enzyme Assays

Matrix Metalloproteinase family including for example MMP12, MMP13.

Recombinant human MMP12 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20:152. The purified enzyme can be used to monitor inhibitors of activity as follows: MMP12 (50 ng/ml final concentration) is incubated for 30 minutes at RT in assay buffer (0.1M Tris-HCl, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.040 mM ZnCl and 0.05% (w/v) Brij 35) using the synthetic substrate Mac-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)]. The purified enzyme can be used to monitor inhibitors of activity as follows: purified proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM CaCl2, 0.02 mM ZnCl and 0.05% (w/v) Brij 35) using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH_2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

A similar protocol can be used for other expressed and purified pro MMPs using substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family including for example TNF convertase

The ability of the compounds to inhibit proTNFα convertase enzyme may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 18 hours. The amount of inhibition is determined as for MMP13 except λex 490nm and λem 530nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; Ser^1(But), Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosures of E. C. Arner *et al.*, (1998) Osteoarthritis and Cartilage 6:214-228; (1999) Journal of Biological Chemistry, 274 (10), 6594-6601 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of metalloproteinase activity in cell/tissue based activity

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNFα production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNFα production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNFα. Heparinized (10Units/ml) human blood obtained from volunteers is diluted 1:5 with medium (RPMI1640 + bicarbonate, penicillin, streptomycin and glutamine) and incubated (160μl) with 20μl of test compound (triplicates), in DMSO or appropriate vehicle, for 30

min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20µl LPS (E. coli. 0111:B4; final concentration 10µg/ml). Each assay includes controls of diluted blood incubated with medium alone (6 wells/plate) or a known TNFα inhibitor as standard. The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100µl) and stored in 96 well plates at -70°C before subsequent analysis for TNFα concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

Pharmacodynamic test

To evaluate the clearance properties and bioavailability of the compounds of this invention an ex vivo pharmacodynamic test is employed which utilises the synthetic substrate assays above or alternatively HPLC or Mass spectrometric analysis. This is a generic test which can be used to estimate the clearance rate of compounds across a range of species. Animals (e,g. rats, marmosets) are dosed iv or po with a soluble formulation of compound (such as 20% w/v DMSO, 60% w/v PEG400) and at subsequent time points (e.g. 5, 15, 30, 60, 120, 240, 480, 720, 1220 mins) the blood samples are taken from an appropriate vessel into 10U heparin. Plasma fractions are obtained following centrifugation and the plasma proteins precipitated with acetonitrile (80% w/v final concentration). After 30 mins at -20°C the plasma proteins are sedimented by centrifugation and the supernatant fraction is evaporated to dryness using a Savant speed vac. The sediment is reconstituted in assay buffer and subsequently analysed for compound content using the synthetic substrate assay. Briefly, a compound concentration-response curve is constructed for the compound undergoing evaluation. Serial dilutions of the reconstituted plasma extracts are assessed for activity and the amount of compound present in the original plasma sample is calculated using the concentration-response curve taking into account the total plasma dilution factor.

In vivo assessment

Test as an anti-TNF agent

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors is assessed in the rat. Briefly, groups of male Wistar Alderley Park (AP) rats (180-210g) are dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.). Ninety minutes later rats are sacrificed using a rising concentration of CO_2 and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples are immediately placed on ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood. The rat plasma samples are thawed and 175µl of each sample are added to a set format pattern in a 96U well plate. Fifty µl of heparinized human blood is then added to each well, mixed and the plate is incubated for 30 min at 37°C (humidified incubator). LPS (25µl; final concentration 10µg/ml) is added to the wells and incubation continued for a further 5.5 hours. Control wells are incubated with 25µl of medium alone. Plates are then centrifuged for 10 min at 2000 rpm and 200µl of the supernatants are transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

$$\text{Percent inhibition of TNF}\alpha = \frac{\text{Mean TNF}\alpha\text{ (Controls)} - \text{Mean TNF}\alpha\text{ (Treated)} \times 100}{\text{Mean TNF}\alpha\text{ (Controls)}}$$

Test as an anti-arthritic agent

Activity of a compound as an anti-arthritic is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146,:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

Test as an anti-cancer agent

Activity of a compound as an anti-cancer agent may be assessed essentially as described in I. J. Fidler (1978) Methods in Cancer Research 15:399-439, using for example the B16 cell line (described in B. Hibner *et al.*, Abstract 283 p75 10th NCI-EORTC Symposium, Amsterdam June 16 – 19 1998).

Test as an anti-emphysema agent

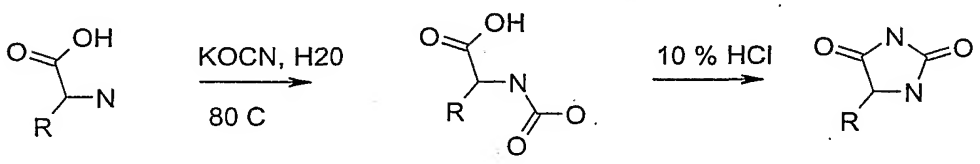
Activity of a compound as an anti-emphysema agent may be assessed essentially as described in Hautamaki *et al* (1997) Science, 277: 2002.

The invention will now be illustrated but not limited by the following Examples:

Preparation of starting materials

According to Scheme 4 below, the hydantoins **5** were prepared in two steps from general amino acids **3** with isolation of the intermediates **4**.

Scheme 4



3 **4** **5**

Table 1 lists some of the starting materials, **5**, that were synthesized. The general method of preparation was as follows. A slurry of amino acid **3** (25 mmol) and potassium cyanate (5.1 g, 63 mmol) in water (75 ml) was heated at 80°C for approximately 1 hour. The clear solution was cooled to 0°C and acidified to approximately pH 1 with concentrated hydrochloric acid (aq). The resulting white precipitate **4** was heated at reflux for 0.5-1 hour and then cooled on ice. In some instances full conversion was not reached

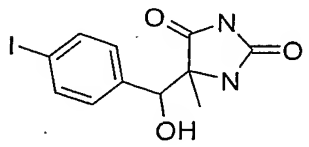
after 1 hour heating. In these cases the crude material was treated under the same protocol again. The white solid was filtered, washed with water, dried and analysed by HNMR and LCMS.

Table 1: Starting materials

Compounds **5** in Scheme 4	Yield (%)	APCI-MS m/z: [MH^+]
5-(4-Chloro-benzyl)-imidazolidine-2,4-dione	87	224.9
[3-(2,5-Dioxo-imidazolidin-4-yl)-propyl]-carbamic acid benzyl ester	50	292.0
5-Isobutyl-imidazolidine-2,4-dione	85	157.0
5-Methylsulfanylmethyl-imidazolidine-2,4-dione	45	161.0
5-sec-Butyl-imidazolidine-2,4-dione	52	157.0
5-(2-Hydroxy-ethyl)-imidazolidine-2,4-dione	36	

EXAMPLE 1

5-[Hydroxy-(4-iodo-phenyl)-methyl]-5-methyl-imidazolidine-2,4-dione



4-Iodo-benzaldehyde (9.280 g, 40.0 mmol), 5-methyl-hydantoin (4.564 g, 40.0 mmol) and 45 % aqueous trimethylamine (6.40 ml, 40.0 mmol) was heated at reflux in ethanol (60 ml) and water (40 ml) for 20 hours under an atmosphere of nitrogen. A white precipitate was formed. After cooling at room temperature for approximately 15 minutes the precipitate was collected by filtration, washed sequentially with ethanol (50%, 50 ml), water (50 ml)

and diethyl ether (50 ml). Drying by air suction afforded the title compound (7.968 g, 23.0 mol) in 57.5 % yield as white solid in form of a pure diastereoisomer.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.19 (1H, s); 8.08 (1H, s); 7.64 (2H, d, J = 8.6Hz); 7.07 (2H, d, J = 8.4 Hz); 5.98 (1H, d, J = 4.5 Hz); 4.57 (1H, d, J = 4.3 Hz); 1.40 (3H, s). APCI-MS m/z: 346.9 [MH^+].

Chromatographic resolution:

A portion of 0.158 g diastereomerically pure 5-(hydroxy-(4-iodophenyl)-methyl)-5-methyl-imidazolidine-2,4-dione was dissolved in 205 mL absolute ethanol/ *iso*-hexane (50:50) and filtered through a 0.45 µm nylon filter. Volumes of 5.0 mL were injected repeatedly on a chiral column (Chiralpak AD-H (2 cm ID x 25 cm L)) connected to a UV-detector (254 nm) and fraction collector. Separation was performed with absolute ethanol/ *iso*-hexane (50:50) as eluant at 6.0 mL/min flow and the pure enantiomers eluted. Fractions containing the same enantiomer were combined, concentrated and assessed for optical purity by chiral chromatography (see below).

Enantiomer A ("early" fractions)

Yield: 0.068 g white flakes

Chiral chromatography (Chiralpak AD-H (0.45 cm I.D x 25 cm L) at 0.43 mL/min absolute ethanol/ *iso*-hexane (50:50))

Retention time: 10.5 minutes

Optical purity: 99.9% e.e (no enantiomer B present)

Enantiomer B ("late" fractions)

Yield: 0.071 g white flakes

Chiral chromatography (Chiralpak AD-H (0.45 cm I.D x 25 cm L) at 0.43 mL/min absolute ethanol/ *iso*-hexane (50:50))

Retention time: 12.2 minutes

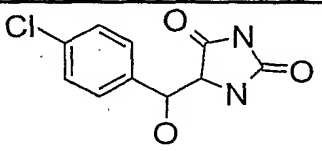
Optical purity: 99.6% e.e (0.24% of enantiomer B present)

The NMR spectra of the pure enantiomers matched that of the pure diastereoisomer.

The following Examples were prepared following the procedure in Example 1. If not otherwise indicated, final compounds represent a mixture of four stereoisomers. Column chromatography was used for final purification or for separation of diastereoisomers.

EXAMPLE 2

5-[(4-Chloro-phenyl)-hydroxy-methyl)]-imidazolidine-2,4-dione



Diastereoisomer A

^{1}H NMR (400 MHz, DMSO-d6): 10.32 (1H, s); 8.07 (1H, s); 7.37 (2H, d, J = 8.5 Hz); 7.30 (2H, d, J = 8.5 Hz); 5.94 (1H, d, J = 3.9 Hz); 4.92 (1H, t, J = 3.2 Hz); 4.35 (1H, dd, J = 3.1,1.0Hz).

^{13}C NMR (400 MHz, DMSO-d6): 173.00; 157.36; 138.41; 131.98; 128.86; 127.52; 71.65; 63.88.

APCI-MS m/z: 241 [MH+].

Diastereoisomer B

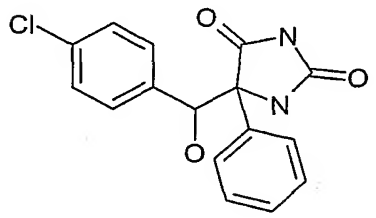
^{1}H NMR (400 MHz, DMSO-d6): 10.53 (1H, s); 7.54 (1H, s); 7.42-7-37 (4H, m); 5.83 (1H, d, J = 5.6 Hz); 4.91 (1H, dd, J = 5.6, 2.6 Hz); 4.23 (1H, dd, J = 2.6,1.5 Hz).

^{13}C NMR (400 MHz, DMSO-d6): 173.97; 158.04; 140.62; 131.67; 128.15; 127.89; 70.08; 63.93.

APCI-MS m/z: 241 [MH+].

EXAMPLE 3

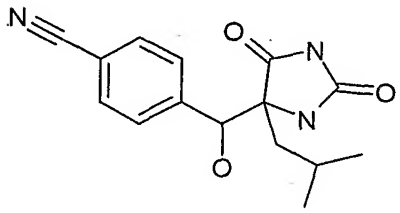
5-[(4-Chloro-phenyl)-hydroxy-methyl]-5-phenyl-imidazolidine-2,4-dione



APCI-MS m/z: 317.1 [MH+].

EXAMPLE 4

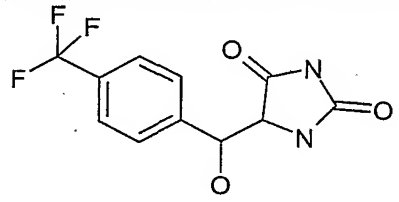
5-[(4-Cyano-phenyl)-hydroxy-methyl]-5-isobutyl-imidazolidine-2,4-dione



APCI-MS m/z: 288.1 [MH+].

EXAMPLE 5

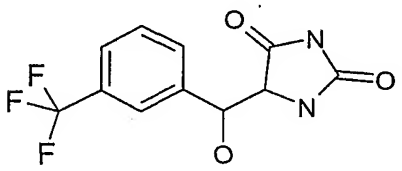
5-[(4-Trifluoromethyl-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 275.1 [MH+].

EXAMPLE 6

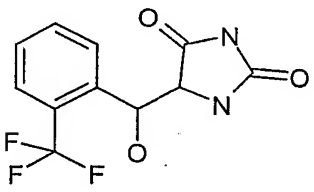
5-[(3-Trifluoromethyl-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 275.2 [MH+].

EXAMPLE 7

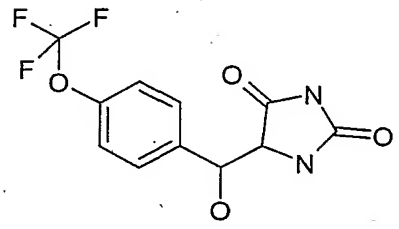
5-[(2-Trifluoromethyl-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 275.1 [MH+].

EXAMPLE 8

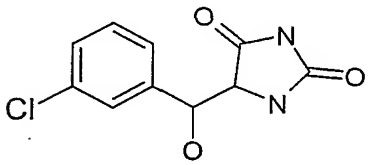
5-[(4-Trifluoromethoxy-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 291.3 [MH+].

EXAMPLE 9

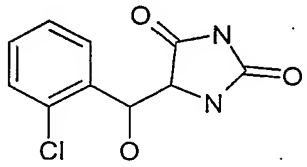
5-[(3-Chloro-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 241.0 [MH+].

EXAMPLE 10

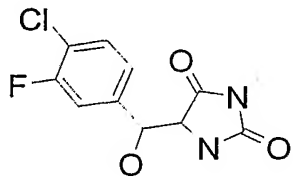
5-[(2-Chloro-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 241.0 [MH+].

EXAMPLE 11

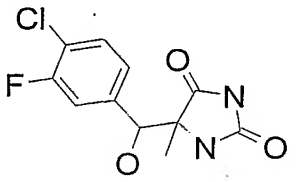
5-[(4-Chloro-3-fluoro-phenyl)-hydroxy-methyl]-imidazolidine-2,4-dione



APCI-MS m/z: 259.0 [MH+]

EXAMPLE 12

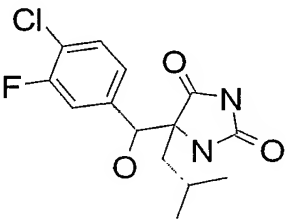
5-[(4-Chloro-3-fluoro-phenyl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione



APCI-MS m/z: 272.9 [MH+]

EXAMPLE 13

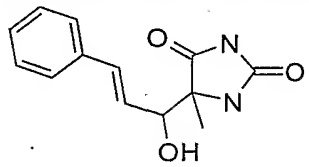
5-[(4-Chloro-3-fluoro-phenyl)-hydroxy-methyl]-5-isobutyl-imidazolidine-2,4-dione



APCI-MS m/z: 315.9 [MH+]

EXAMPLE 14

5-(1-Hydroxy-3-phenyl-allyl)-5-methyl-imidazolidine-2,4-dione

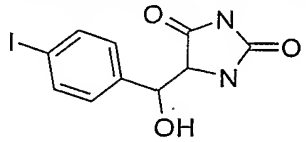


^{1}HNMR (400 MHz, DMSO-d_6): δ 10.45 (1H, s); 7.88 (1H, s); 7.38-7.22 (5H, m); 6.54 (1H, d , J = 16.1 Hz); 6.22 (1H, dd, J = 7.3, 7.6 Hz); 5.56 (1H, d, J = 4.5 Hz); 4.09 (1H, d, J = 3.6, 4.5 Hz); 1.27 (3H, s).

APCI-MS m/z: 247.1 [MH^+].

EXAMPLE 15

5-[Hydroxy-(4-iodo-phenyl)-methyl]-imidazolidine-2,4-dione

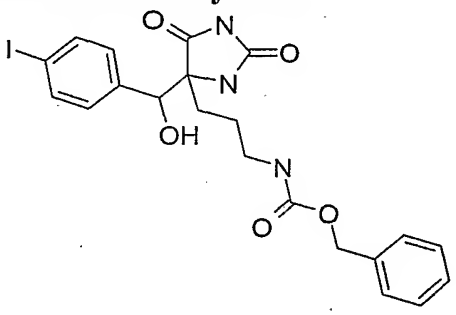


^{1}HNMR (300 MHz, DMSO-d_6): δ 10.32 (1H, s); 8.06 (1H, s); 7.66 (2H, d, J = 8.1 Hz); 7.10 (2H, d, J = 8.3 Hz); 5.91 (1H, d, J = 3.9 Hz); 4.87 (1H, t, J = 2.7 Hz); 4.34 (1H, d, J = 2.5 Hz).

APCI-MS m/z: 333.1 [MH^+].

EXAMPLE 16

(3-{4-[Hydroxy-(4-iodo-phenyl)-methyl]-2,5-dioxo-imidazolidin-4-yl}-propyl)-carbamic acid benzyl ester

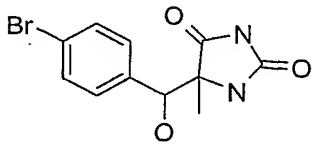


APCI-MS m/z: 524.1 [MH^+].

EXAMPLE 17

5-[(4-Bromo-phenyl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-Methyl-imidazolidine-2,4-dione.



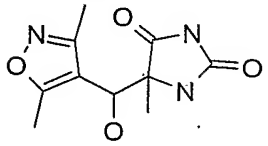
^1H NMR (400 MHz, DMSO-d6): δ 10.18 (1H, s); 8.08 (1H, s); 7.46 (2H, d, J=8.4Hz); 7.20 (2H, d, J=8.4 Hz); 5.99 (1H, d, J=4.4 Hz); 4.59 (1H, d, 3.81 Hz); 1.39 (3H, s).

APCI-MS m/z: 298.9 [MH^+]

EXAMPLE 18

5-[(3,5-Dimethyl-isoxazol-4-yl)-hydroxy-methyl]-5-methyl-imidazolidine-2,4-dione

Produced by aldol condensation of 3,5-dimethyl-isoxazole-4-carbaldehyde and 5-Methyl-imidazolidine-2,4-dione.

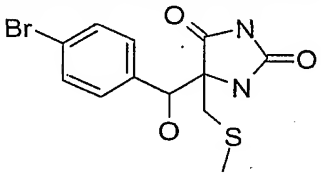


APCI-MS m/z: 240 [MH^+]

EXAMPLE 19

5-[(4-Bromo-phenyl)-hydroxy-methyl]-5-methylsulfanylmethyl-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-methylsulfanylmethyl-imidazolidine-2,4-dione.

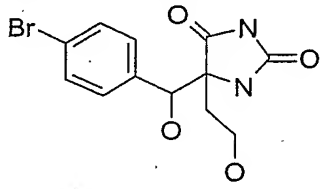


APCI-MS m/z: 347.1 [MH^+]

EXAMPLE 20

5-[(4-Bromo-phenyl)-hydroxy-methyl]-5-(2-hydroxy-ethyl)-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-(2-hydroxy-ethyl)-imidazolidine-2,4-dione.

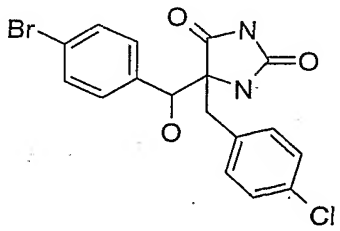


APCI-MS m/z: 311.2 [MH^+ -H_2O]

EXAMPLE 21

5-[(4-Bromo-phenyl)-hydroxy-methyl]-5-(4-chloro-benzyl)-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-(4-chloro-benzyl)-imidazolidine-2,4-dione.

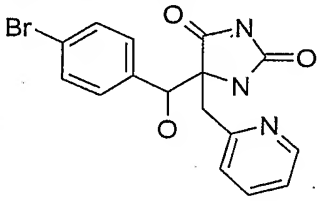


APCI-MS m/z: 411 [MH^+]

EXAMPLE 22

5-[(4-Bromophenyl)hydroxy-methyl]-5-pyridine-2-ylmethyl-imidazolidine-2,4-dione

Produced by aldol condensation of 4-bromo-benzaldehyde and 5-pyridine-4-ylmethyl-imidazolidine-2,4-dione.

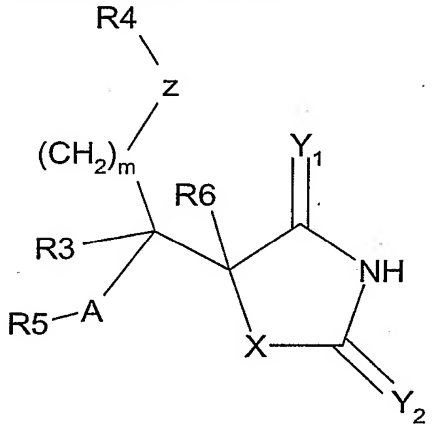


APCI-MS m/z: 378.1 [MH^+]

CLAIMS:

What we claim is:

1. A compound of the formula I or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof



I

wherein

X is selected from NR1, O, S;

Y1 and Y2 are independently selected from O, S;

Z is selected from NR2, O, S;

m is 0 or 1;

A is selected from a direct bond, (C1-6)alkyl, (C1-6)alkenyl, (C1-6)haloalkyl, or (C1-6)heteroalkyl containing a hetero group selected from N, O, S, SO, SO2 or containing two hetero groups selected from N, O, S, SO, SO2 and separated by at least two carbon atoms;

R1 is selected from H, alkyl, haloalkyl;

R2 is selected from H, alkyl, haloalkyl;

R3 and R6 are independently selected from H, halogen (preferably F), alkyl, haloalkyl, alkoxyalkyl, heteroalkyl, cycloalkyl, aryl, alkylaryl, heteroalkyl-aryl, heteroaryl, alkylheteroaryl, heteroalkyl-heteroaryl, arylalkyl, aryl-heteroalkyl, heteroaryl-alkyl, heteroaryl-heteroalkyl, bisaryl, aryl-heteroaryl, heteroaryl-aryl, bisheteroaryl, cycloalkyl or heterocycloalkyl comprising 3 to 7 ring atoms, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl radicals may be optionally substituted by one or

more groups independently selected from hydroxy, alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, carboxy, carboxyalkyl, alkylcarboxy, amino, N-alkylamino, N,N-dialkylamino, alkylamino, alkyl(N-alkyl)amino, alkyl(N,N-dialkyl)amino, amido, N-alkylamido, N,N-dialkylamido, alkylamido, alkyl(N-alkyl)amido, alkyl(N,N-dialkyl)amido, thiol, sulfone, sulfonamino, alkylsulfonamino, arylsulfonamino, sulfonamido, haloalkyl sulfone, alkylthio, arylthio, alkylsulfone, arylsulfone, aminosulfone, N-alkylaminosulfone, N,N-dialkylaminosulfone, alkylaminosulfone, arylaminosulfone, cyano, alkylcyano, guanidino, N-cyano-guanidino, thioguanidino, amidino, N-aminosulfon-amidino, nitro, alkylnitro, 2-nitro-ethene-1,1-diamine;

R4 is selected from H, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, haloalkoxy, aminoalkyl, amidoalkyl, thioalkyl;

R5 is a monocyclic group comprising 3 to 7 ring atoms independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl, optionally substituted by one or more substituents independently selected from halogen, hydroxy, haloalkoxy, amino, N-alkylamino, N,N-dialkylamino, cyano, nitro, alkyl, alkoxy, alkyl sulfone, haloalkyl sulfone, carbonyl, carboxy, wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, alkylcarboxyamino, cyano, nitro, thiol, alkylthiol, alkylsulfono, alkylaminosulfono, alkylcarboxylate, amido, N-alkylamido, N,N-dialkylamido, alkoxy, haloalkoxy, carbonyl, carboxy;

Provided that:

when X is NR1, R1 is H, Y1 is O, Y2 is O, Z is O, m is 0, A is a direct bond, R3 is H, R4 is H and R6 is H, then R5 is not phenyl, nitrophenyl, hydroxyphenyl, alkoxyphenyl or pyridine;

when X is NR1, R1 is H or methyl, Y1 is O, Y2 is O, Z is O, m is 0, A is a direct bond, R3 is H, R4 is H and R6 is phenyl, then R5 is not phenyl;

when X is NR1, R1 is H, Y1 is O, Y2 is O, Z is O, m is 0, A is a direct bond, R3 is phenyl, R4 is H and R6 is H, then R5 is not phenyl;

when X is S, at least one of Y1 and Y2 is O, m is 0, A is a direct bond, R3 is H or methyl, R6 is H or methyl, then R5 is not phenyl, pyridine, pyrrole, thiophen or furan;

when X is O, Y1 is O, Y2 is O, Z is O, m is 0, A is a direct bond, R3 is methylchloride, R4 is H and R6 is H, then R5 is not phenyl.

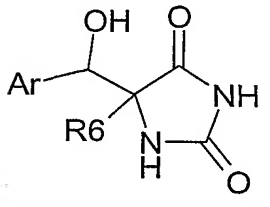
2. A compound of the formula I as claimed in claim 1 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof, wherein X is NR1, R1 is H or (C1-3) alkyl, at least one of Y1 and Y2 is O, Z is O, m is 0, and A is a direct bond.

3. A compound as claimed in either claim 1 or claim 2 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof, wherein R3 is H, alkyl or haloalkyl, R4 is H, alkyl or haloalkyl.

4. A compound as claimed in any of the preceding claims or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof, wherein R5 is an optionally substituted 5 or 6 membered ring independently selected from cycloalkyl, aryl, heterocycloalkyl or heteroaryl.

5. A compound as claimed in any of the preceding claims or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof, wherein R6 is H, alkyl, hydroxyalkyl, aminoalkyl, cycloalkyl-alkyl, alkyl-cycloalkyl, arylalkyl, alkylaryl, heteroalkyl, heterocycloalkyl-alkyl, alkyl-heterocycloalkyl, heteroaryl-alkyl or heteroalkyl-aryl.

6. A compound of the formula II or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof



Formula II

wherein

Ar is a 5 or 6 membered aryl or heteroaryl group optionally substituted by one or two substituents selected from halogen, amino, nitro, (C1-6)alkyl, (C1-6)alkoxy or (C1-6) haloalkoxy;

R6 is selected from H, aryl or (C1-6)alkyl and R6 is optionally substituted by a group selected from hydroxy, thioalkyl, phenyl, halophenyl, pyridyl or carbamate.

7. A compound of the formula II as claimed in claim 6 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof, wherein Ar is phenyl or substituted phenyl, or Ar is a 5-membered heteroaryl ring comprising two heteroatoms independently selected from O and N.

8. A compound of the formula II as claimed in either claim 6 or claim 7 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof wherein R6 is phenyl, phenyl substituted with a halogen, methylene pyridine, or (C1-3)alkyl optionally substituted with hydroxy, thiomethyl or benzyl carbamate.

9. A pharmaceutical composition which comprises a compound of the formula I as claimed in claim 1 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition which comprises a compound of the formula II as claimed in claim 6 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

11. A method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a compound of the formula I or formula II or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

12. Use of a compound of the formula I or formula II or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes.

INTERNATIONAL SEARCH REPORT

Inte...nal application No.
PCT/SE 02/00474

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 233/78, C07D 401/06, C07D 413/06, A61K 31/4166, A61K 31/444, A61P 35/00, A61P 11/00, A61P 19/00, A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9906361 A2 (ABBOTT LABORATORIES), 11 February 1999 (11.02.99) --	1-12
A	WO 0040577 A1 (AVENTIS PHARMACEUTICALS INC.), 13 July 2000 (13.07.00) --	1-12
A	EP 0640594 A1 (FUJIREBIO INC.), 1 March 1995 (01.03.95) --	1-12

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2002	15 -07- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer EVA JOHANSSON/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Int[illegible]nal application No.
PCT/SE02/00474

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☒ Claims Nos.: 1-5
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II ***Observations where unity of invention is lacking (Continuation of item 2 of first sheet)***

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*
Claim 11 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

**

Present claims 1-5 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims, which appear to be supported, and disclosed, namely those parts related to the compounds according to the examples in the description.

INTERNATIONAL SEARCH REPORT

Intern application No.
PCT/SE 02/00474

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9906361 A2	11/02/99	AU 8513998 A	22/02/99
		BG 103995 A	31/07/00
		BR 9810760 A	27/11/01
		CN 1261876 T	02/08/00
		EP 1001930 A	24/05/00
		HU 0002037 A	28/05/01
		JP 2001523272 T	20/11/01
		NO 996579 A	24/01/00
		NZ 501166 A	21/12/01
		PL 337854 A	11/09/00
		SK 170599 A	16/05/00
		TR 9903287 T	00/00/00
		ZA 9806828 A	29/01/99
WO 0040577 A1	13/07/00	AU 1817700 A	24/07/00
		EP 1150975 A	07/11/01
EP 0640594 A1	01/03/95	JP 7126258 A	16/05/95